APPENDIX A. TOXICITY SUMMARIES

ACETALDEHYDE
CAS No: 75-07-0

INTRODUCTION

Acetaldehyde is directly emitted into the atmosphere as a product of incomplete combustion. It is also formed in the atmosphere as a result of photochemical oxidation of hydrocarbons and free radical reactions involving hydroxyl radicals. Photochemical oxidation is estimated to contribute 56% of the ambient acetaldehyde, as predicted by the Urban Airshed model. Concentrations of acetaldehyde formed via photochemical oxidation can vary significantly depending on the season, location, meteorological conditions, and time of day. Reactive organic gases such as ethyl peroxide and ethoxy radicals are precursors of photochemically generated acetaldehyde, while products of its atmospheric degradation include formaldehyde and peroxyacetyl nitrate (PAN). Acetaldehyde is regulated in California as a Toxic Air Contaminant, and is monitored by the statewide California Air Resources Board (CARB) toxics monitoring network.

KEY TOXICOLOGIC EFFECTS

Acute Toxicity

Acute exposure to acetaldehyde vapor leads to eye, skin and respiratory tract irritation (Reprotext, 1997). Eye irritation has occurred at airborne concentrations as low as 45 mg/m^3 and is seen in all persons exposed to 360 mg/m^3 (Clayton and Clayton, 1993; Grant, 1993). With higher airborne concentrations or extended exposure, corneal epithelium damage may occur producing photophobia, a foreign body sensation, and persistent lacrimation (Clayton and Clayton, 1993; HSDB, 1999). Concentrations of 12 $\mu g/m^3$ in air have caused changes in light sensitivity of the eye (Grant, 1993). Changes in auditory sensitivity were noted in one study at airborne exposure levels of approximately 50 $\mu g/m^3$ (Grant, 1993). Exposure to an airborne concentration of 241 mg/m^3 for 30 minutes resulted in upper respiratory tract irritation (Hathaway et al., 1991). Acetaldehyde may also cause bronchitis. Acetaldehyde exposure decreased pulmonary macrophage number (Clayton and Clayton, 1993). Higher concentrations can cause a build-up of fluid in the lungs (pulmonary edema), with severe shortness of breath.

Chronic Toxicity

No epidemiological exposure studies were located that specifically examined the effects of acetaldehyde in humans. In experimental animals, chronic exposure has caused growth retardation, upper respiratory tract irritation, mild anemia, increased urinary glutamic-oxaloacetic transaminase (SGOT/AST) activity, increased urinary protein content, increased kidney weights (without renal pathology), and histopathological changes in the nasal mucosa and trachea (including hyperplasia, squamous metaplasia, and inflammation) (ACGIH, 1991; Hathaway et al., 1991). Rats exposed to high concentrations (> 2880 mg/m^3) exhibited acute

bronchopneumonia, occasionally accompanied by tracheitis and severe respiratory distress that included salivation, labored breathing, and mouth breathing.

Carcinogenicity

An increased incidence of nasal tumors in rats and laryngeal tumors in hamsters has been observed following inhalation exposure to acetaldehyde. The International Agency for Research on Cancer (IARC) classified acetaldehyde in Group 2B, possible human carcinogen, based on sufficient evidence in animals and inadequate evidence in humans (IARC, 1987). U.S. EPA (1997a) classified acetaldehyde in Group B2, probable human carcinogen, on the basis of sufficient evidence for carcinogenicity in animals and inadequate evidence in humans. OEHHA (1993) developed a cancer unit risk value of 2.7×10^{-6} $(\mu g/m^3)^{-1}$ for acetaldehyde under the Toxic Air Contaminant program. Acetaldehyde is listed as a carcinogen by the State of California under Proposition 65, California's Safe Drinking Water and Toxic Enforcement Act of 1986.

Reproductive and Developmental Toxicity

No information is available regarding adverse reproductive or developmental effects of acetaldehyde in humans (U.S. EPA, 1994b). In studies with rodents, acetaldehyde has been shown to cross the placenta and cause growth retardation, to cause skeletal malformations, and to kill embryos. *In vitro* reproductive toxicity studies have shown that acetaldehyde is an inhibitor of testicular testosterone production (OEHHA, 1993). Acetaldehyde is not listed as a reproductive or developmental toxicant by the State of California under Proposition 65.

DOSE-RESPONSE ASSESSMENT

The following table contains available health assessment values used by California regulatory programs for acetaldehyde.

Table 1. Health assessment values for acetaldehyde

	Health Assessment Value	Reference
Acute reference exposure level (REL)	NA	---
Chronic reference exposure level (REL)*	9 $\mu g/m^3$	OEHHA (1993)
Cancer potency factor	1.0×10^{-2} $(mg/kg\text{-}day)^{-1}$	OEHHA (1999b)
Unit risk factor	2.7×10^{-6} $(\mu g/m^3)^{-1}$	OEHHA (1999b)
No significant risk level (NSRL)	90 µg/day	OEHHA (1994b)
U.S. EPA reference dose (RfD)	NA	---
U.S. EPA reference concentration (RfC)	9 $\mu g/m^3$	U.S. EPA (1991)
Public health goal	NA	---

** This chronic REL was adopted from the Toxic Air Contaminant document approved by the Scientific Review Panel in 1993.*
NA = not available

Since adopted health assessment values suitable for assessing potential health impacts from short-term inhalation exposures are not available for acetaldehyde, OEHHA calculated a draft health protective concentration (HPC) for the purpose of this report. In calculating the HPC, OEHHA followed the risk assessment methodology used for developing the acute reference exposure levels (RELs) under the Air Toxics Hot Spots Program risk assessment guidelines process (OEHHA, 1999a). As mandated by state legislation, these guidelines underwent scientific and public peer review, prior to approval by the Scientific Review Panel (Senate Bill 1731, Statutes of 1992, Ch. 1162 of the California Health and Safety Code) and adoption by OEHHA. The derivation of the HPC is summarized below. Further details on the methodology are provided in OEHHA (1999a).

Derivation of Health Protective Concentration

Silverman et al. (1946) found that a 15-minute exposure to acetaldehyde induced eye irritation in male and female human volunteers at a concentration of 46 mg/m^3 (26 ppm). This concentration was identified as a lowest-observed-adverse-effect level (LOAEL); a no-observed-adverse-effect level (NOAEL) was not observed in this study. Application of "Haber's Law" to extrapolate from a 15 minute exposure to 1 hour results in an adjusted LOAEL of 11.5 mg/m^3 (6.5 ppm), as shown below.

$$C^nT = K$$
$$C^n{}_1T_1 = C^n{}_2T_2 \text{ where n=1 for extrapolation from 15 min. to 60 min.}$$
$$(46 \text{ mg/m}^3)(15 \text{ min}) = (C)(60 \text{ min})$$
$$C = 11.5 \text{ mg/m}^3$$

An acute 1-hour draft HPC can be calculated for acetaldehyde using the formula:

$$\text{Draft HPC} = \text{LOAEL} / \text{UF} = 11.5 \text{ mg/m}^3 / 100 = 115 \text{ } \mu\text{g/m}^3 \text{ (65 ppb)}$$

The uncertainty factor (UF) for this calculation is 100, which incorporates uncertainty contributions for extrapolation from a LOAEL to a NOAEL (10) and for potentially sensitive human subpopulations (10).

BENZENE
CAS No.: 71-43-2

INTRODUCTION

Except for cigarette smoking, vaporization of gasoline and automobile exhaust are the primary sources of benzene exposure in the general population (Wallace, 1996). Past formulations of gasoline contained about one to two percent benzene; however, current formulations are required to contain no more than one percent benzene by volume (CARB, 1997; CARB, 1998).

The California Air Resources Board (CARB) routinely monitors ambient air concentrations of benzene throughout California through its air toxics network. In 1982, when the monitoring program began, estimates of the population-weighted annual concentration of benzene was roughly 5 ppb (16 $\mu g/m^3$) (CARB, 1984). These concentrations have declined steadily over time such that in 1994 average estimates across the state were approximately 1.2 ppb (3.8 $\mu g/m^3$) (CARB, 1995). Since the statewide use of oxygenated gasoline in 1996, the ambient air concentrations of benzene have dropped to less than 1 ppb.

In studies of human exposures to benzene, the primary sources of exposure among non-smokers were auto exhaust and gasoline vapor emissions. Most of the benzene in outdoor air comes from auto and gasoline vapor emissions; inhalation of ambient air accounts for a large percentage of an individual's total benzene exposure. Also, indoor air exposures due to intrusion of evaporative gasoline fumes in homes with attached garages and personal activities such as driving can contribute significantly to an individual's total exposure to benzene (Wallace, 1996). Other sources of exposure to benzene include contaminated drinking water, which can arise for example from contamination of water sources by leaking from underground fuel storage tanks. In addition to direct ingestion, exposure routes of concern for benzene-contaminated drinking water include inhalation and dermal absorption from showering, cooking, and other household activities.

KEY TOXICOLOGIC EFFECTS

Acute Toxicity

Exposure to air concentrations of benzene of approximately 20,000 ppm for five to ten minutes, 7500 ppm for 30 minutes, or 1500 ppm for 60 minutes is estimated to cause death or severe toxicity in humans. Causes of death include pulmonary hemorrhage, renal congestion, and cerebral edema. Acute exposures to benzene have also resulted in less severe symptoms including headaches, lethargy, and weakness. These symptoms have been reported from exposure to 50 to 150 ppm benzene for 5 hours, whereas exposure to 25 ppm for eight hours showed no clinical effect (IPCS, 1993; Paustenbach et al., 1993).

Chronic Toxicity

Long-term exposure of humans to benzene is associated with numerous adverse effects including bone marrow damage, changes in circulating blood cells, developmental and reproductive effects, immunological effects, mutation, chromosomal damage, and cancer.

In humans, the blood forming organs (i.e., the lymphohematopoietic system) appear to be the most sensitive to the toxic effects of benzene. Many blood disorders, including aplastic anemia, pancytopenia, thrombocytopenia, granulocytopenia, lymphocytopenia, and leukemia have been associated with chronic exposure to inhaled benzene. Statistically significant increases in myelodysplastic syndromes and acute non-lymphocytic leukemia have been observed among workers exposed to average air concentrations of less than 10 ppm benzene (Hayes et al., 1997; OEHHA, 1999e).

Carcinogenicity

Benzene has been clearly established as a known human carcinogen. In 1987, benzene was listed as a carcinogen by the State of California under Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986. The International Agency for Research on Cancer (IARC) has classified benzene as Group 1, known to be carcinogenic to humans (IARC, 1982). U.S. EPA classifies benzene as a Group A, human carcinogen (U.S. EPA, 1999a).

The carcinogenic activity of benzene in humans has been established through numerous occupational epidemiological studies and case series reports. It is well established that benzene can cause acute myelogenous leukemia and myelodysplastic syndromes. Strong evidence exists to implicate benzene in causing other forms of leukemia as well. There is some evidence to suggest that benzene also causes lymphoma and multiple myeloma in humans but these associations are less clear. Benzene has also been implicated as a potential risk factor for childhood leukemia (OEHHA, 1997b; Smith and Zhang, 1998).

Benzene also has been shown to be carcinogenic in numerous animal studies by either the inhalation or oral route of administration. Statistically significant increased incidences of cancer were observed at multiple sites, including Zymbal gland, mammary gland, ovary, uterus, nasal cavity, oral cavity, skin, Harderian gland, preputial gland, liver, and lung. Leukemias and lymphomas were also reported (ATSDR, 1997).

Reproductive and Developmental Toxicity

Benzene causes reproductive and developmental effects including reduced fetal weight, delayed ossification, fetal chromosomal damage, altered fetal hematopoiesis, and alterations to sperm. OEHHA (1997b) extensively reviewed the available literature on benzene's reproductive and developmental toxicity. Benzene was listed in 1997 as a reproductive and developmental toxicant by the State of California under Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986.

DOSE-RESPONSE ASSESSMENT

The following table contains current health assessment values used by California regulatory programs for benzene.

Table 2. Health assessment values for benzene

	Health Assessment Value	Reference
Acute reference exposure level (REL)	1300 µg/m^3 (for 6 hr)	OEHHA (1999a)
Proposed chronic reference exposure level (REL)	60 µg/m^3	OEHHA (1999c)
Cancer potency factor	1.0×10^{-1} (mg/kg-day)$^{-1}$	OEHHA (1994a)
Unit risk factor	2.9×10^{-5} (µg/m^3)$^{-1}$	OEHHA (1994a)
No significant risk level (NSRL)	7 µg/day	DHS (1988)
Proposed maximum contaminant level (PMCL)*	1.8×10^{-4} mg/L	DHS (1987)
Proposed public health goal (PHG)	0.00014 mg/L (0.14 ppb)	OEHHA (1999e)

Adopted health assessment values suitable for estimating potential non-cancer public health impacts from chronic benzene inhalation exposures, as well as any impacts from oral exposures from drinking water, are not available. Therefore, OEHHA used draft numbers developed under other California regulatory programs for the purpose of this report. To quantify non-cancer risks from chronic inhalation exposures, OEHHA used the proposed chronic reference exposure level (REL) currently being developed under the Air Toxics Hot Spots Program risk assessment guidelines process (Senate Bill 1731, Statutes of 1992, Ch. 1162 of the California Health and Safety Code). The methodology used to derive the proposed chronic REL for benzene, as well as the number itself, have undergone an initial round of public and scientific peer review, and are currently being considered by the State's Scientific Review Panel (1999c). In addition, OEHHA used the proposed public health goal (PHG) developed by OEHHA under the California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) to estimate potential health impacts from exposures via drinking water. The proposed PHG for benzene is also currently undergoing scientific and public review and comment. The derivation of both the proposed chronic REL and PHG for benzene is briefly summarized below. More detailed information is provided in OEHHA (1999c) and OEHHA (1999e), respectively.

Derivation of the Proposed Chronic Reference Exposure Level

Tsai et al. (1983) examined hematologic parameters in a population of male workers exposed to benzene in a refinery. This study provided a no-observed-adverse-effect level (NOAEL) of 0.53 ppm. The Tsai et al. study was based on occupational exposures; however, the chronic REL is intended to protect the general public who could be exposed continuously. Therefore, an equivalent time-weighted average concentration (C_{AVE}) was estimated from the observed concentration (C_{OBS}) as follows:

$$C_{AVE} = C_{OBS} \times (10\ m^3/day\ occupational\ exposure\ /\ 20\ m^3/day\ total\ exposure) \times (5\ days\ /\ 7\ days)$$

In addition, an uncertainty factor of ten was applied to account for sensitive human subpopulations. Therefore:

Proposed chronic REL = C_{AVE} / UF = 0.02 ppm (20 ppb; 0.06 mg/m^3; 60 μg/m^3)

Derivation of the Proposed Public Health Goal

The proposed public health goal (C) for benzene in drinking water (in units mg/L) was calculated as follows:

$$C = \frac{BW \times R}{CSF \times L/day} = mg/L$$

where,

BW = Adult body weight (a default of 70 kg)

R = De minimis level for lifetime excess individual cancer risk (a default of 10^{-6})

CSF = Cancer slope factor was estimated from the upper 95 percent confidence limit on the lifetime risk of total leukemia estimated for general population exposure to benzene, 24 hr/d, 365 d/yr. This estimate comes from the geometric mean of estimates derived from two cohorts, the Pliofilm Cohort (Paxton et al., 1994) and the Chinese Worker Cohort (Hayes et al., 1997). The mean lifetime risk estimate (0.050 ppm^{-1}) has been converted to a population-based cancer potency in units of $(mg/kg\text{-}day)^{-1}$:
risk/(mg/kg-d) = (0.050/ppm)*(ppm/3190 μg/m^3 air)*(70 kg)*(1/20 m^3/d)*(1/0.5 absorbed)*(1000 μg/mg) = 0.11, where 70 kg is the standard adult male body weight, and 20 m^3/d is the default estimate for the volume of air inhaled per day. This computation is based on absorption efficiencies of 50 percent for inhalation and 100 percent for oral ingestion of benzene, which were derived from the available literature on benzene uptake and metabolism in humans and animals (Appendix C of OEHHA, 1999e).

L/day = Daily volume of water consumed by an adult. Although the standard default is 2.0 L/day, studies of household use of benzene-contaminated drinking water (Lindstrom et al., 1994; Beavers et al., 1996) indicate that additional exposures via inhalation (e.g., from stripping of benzene to air via showering, dish washing) and via dermal absorption (e.g., bathing, showering) are expected. A best estimate of the daily water consumption equivalents is 4.7 L (Lindstrom et al., 1994, adjusted values). This value is supported by an estimate obtained from CalTox (DTSC, 1999) of 4.6 L-equivalents. This estimate includes adjustments for differences in absorption by route of exposure.

Therefore:

$$C = \frac{70\ kg \times 10^{-6}}{0.11\ (mg/kg\text{-}d)^{-1} \times 4.7\ Leq/day} = 1.4 \times 10^{-4}\ mg/L, \text{ or } 0.14\ ppb$$

The proposed PHG is 0.14 ppb based on carcinogenicity (total leukemia) which is also protective of non-cancer hematological effects from chronic exposure.

BUTADIENE
1,3-butadiene; CAS No.: 106-99-0

INTRODUCTION

Butadiene is an important industrial chemical used in the production of styrene-butadiene copolymers (SBR rubber) and chloroprene/neoprene. It is primarily released into the environment via emissions from gasoline- and diesel-powered vehicles and equipment. Lesser releases occur via production processes (fugitive leaks), tobacco smoke, gasoline vapors, burning plastic or rubber, and occasionally drinking water (Miller, 1978).Butadiene has low solubility in water, thus environmental release results primarily in air contamination. Airborne butadiene is subject to photodegradation and reaction with ozone and nitrate radicals. The main photooxidation products are acrolein and formaldehyde (Maldotti et al., 1980). Butadiene is regulated in California as a Toxic Air Contaminant, and is routinely monitored by CARB's statewide toxics monitoring network. The mean concentration of butadiene in 1996, as monitored by CARB from January through December of that year, was 0.214 ppb.

KEY TOXIC EFFECTS

Acute Toxicity

Butadiene is only mildly acutely toxic. In rats and mice, the median lethal concentrations (LC_{50}) for butadiene are above 100,000 ppm for two to four hours inhalation. The oral LD_{50} values for rats and mice are 5480 mg/kg and 3210 mg/kg, respectively. Acutely toxic effects of butadiene exposure in experimental animals progressed from light anesthesia, to running movements and tremors, to deep anesthesia and death (NIOSH, 1991).

Chronic Toxicity

Among workers in the styrene-butadiene rubber manufacturing industry, chronic exposure to butadiene was reported to contribute to an increase in overall mortality, emphysema, and cardiovascular diseases in a retrospective epidemiological study (McMichael et al., 1976). In another study, a survey of rubber workers exposed to a mean concentration of 20 ppm butadiene exhibited slightly lower levels (but within normal range) of red blood cells, hemoglobin, platelets, and neutrophils (Checkoway and Williams, 1982). Workers in both of these studies were exposed to mixtures of chemicals. Therefore, the specific contribution of butadiene to the adverse respiratory and hematopoietic effects remain unclear.

In a comprehensive study conducted by the National Toxicology Program, chronic inhalation exposure of mice to concentrations as low as 20 ppm 1,3-butadiene resulted in decreased survival, primarily due to the development of malignant neoplasms (NTP, 1993). Exposure to higher concentrations (60-650 ppm) resulted in significant changes in hematological parameters (i.e., decreased erythrocyte counts, hemoglobin concentrations and packed cell volume); these changes were attributed to significant adverse effects on the bone marrow. In addition to

changes in bone marrow, adverse non-neoplastic or pre-neoplastic effects were observed in liver, thymus, lung, testes, ovary, heart, mammary gland, upper respiratory tract, and other organs.

Carcinogenicity

Results of epidemiological studies regarding the effects of butadiene on human populations have shown an association between butadiene exposure and the occurrence of leukemias (Santos-Burgoa et al., 1992; Matanoski et al., 1993; Delzell et al., 1995 and 1996).

In mice and rats, inhalation of butadiene has been shown to induce tumors at multiple sites (OEHHA, 1992b; 1999b). These sites include heart, lung, mammary gland, ovaries, forestomach, liver, pancreas, Zymbal gland, thyroid, testes, and hematopoietic system (NTP, 1993; Melnick et al., 1990a, 1990b, 1990c; Melnick and Huff, 1992; Owen et al., 1987). Butadiene is only one of two chemicals known to induce cancer of the heart in laboratory animals.

The Occupational Safety and Health Administration (OSHA, 1990) has classified butadiene as a "potential occupational carcinogen". U.S. EPA (1985) and IARC (1987) have concluded that the evidence for carcinogenicity of butadiene in animals is sufficient. These organizations have classified the chemical as Group B2 and 2B, respectively, in their schemes of ranking potential human carcinogens (OEHHA, 1999b).

Reproductive/Developmental Toxicity

No reproductive or developmental toxicity studies were located that specifically examined the effects of butadiene in humans. However, butadiene has been shown to cause reproductive and developmental effects in rodents (OEHHA, 1992b). Reproductive effects have been reported in male and female mice (i.e., testicular and ovarian atrophy, respectively) (NTP, 1993). Developmental effects reported in the literature consist primarily of reduced fetal body weight (observed in both rats and mice) and minor skeletal defects (i.e., abnormal ossifications, abnormal sternebrae, and supernumerary ribs) observed in mice (IISRP, 1982; Hackett et al., 1987b; Anderson et al., 1993). In a 1992 review of the available literature by OEHHA, the no-observed-adverse-effect level (NOAEL) for developmental toxicity in rats was found to be 1000 ppm, while a NOAEL could not be determined for mice since effects were seen in the lowest doses of all available studies (OEHHA, 1992b).

Dose-Response Assessment

The following table contains health assessment values used by California regulatory programs for 1,3-butadiene.

Table 3. Health assessment values for 1,3-butadiene.

	Health Assessment Value	Reference
Acute reference exposure level (REL)	NA	---
Proposed chronic reference exposure level (REL)	8 $\mu g/m^3$	OEHHA (1999c)
Cancer potency factor	3.4 E+0 $(mg/kg\text{-}day)^{-1}$	OEHHA (1999b)
Unit risk factor	1.7×10^{-4} $(\mu g/m3)^{-1}$	OEHHA (1999b)
No significant risk level (NSRL)	0.4 μg/day	OEHHA (1989)
U.S. EPA reference dose (RfD)	NA	--
U.S. EPA reference concentration (RfC)	NA	--
Public health goal (PHG)	NA	---

NA = not available

Since adopted health assessment values suitable for assessing potential non-cancer health impacts from short-term inhalation exposures to butadiene are not available, OEHHA calculated draft health protective concentration (HPC) for the purpose of this report. In calculating the HPC, OEHHA followed the risk assessment methodology used for developing the acute reference exposure levels (RELs) under the Air Toxics Hot Spots Program risk assessment guidelines process (OEHHA, 1999a). As mandated by state legislation, these guidelines underwent scientific and public peer review, prior to approval by the Scientific Review Panel (Senate Bill 1731, Statutes of 1992, Ch. 1162 of the California Health and Safety Code). In addition, in the absence of an adopted health assessment value suitable for assessing chronic inhalation exposures, OEHHA used the proposed chronic reference exposure level (REL) to assess potential public health impacts from chronic inhalation exposures. Chronic RELs are being developed under the legislatively mandated Air Toxics Hot Spots Program risk assessment guidelines process; however, the chronic RELs have not been adopted at this time. The methodology used to derive the proposed chronic REL for butadiene, as well as the number itself, have undergone an initial round of public and scientific peer review, and are currently being considered by the State's Scientific Review Panel (1999c). The derivation of the draft HPC and the proposed chronic REL are summarized below. The adopted risk assessment methodology used for deriving the HPC is provided in OEHHA (1999a), and a more detailed analysis of the chronic REL is provided in OEHHA (1999c).

Derivation of Health Protective Concentration

The short-term inhalation value for butadiene is derived from developmental and reproductive studies evaluated by U.S. EPA (1998). Hackett *et al.* (1987a and b) examined the developmental toxicity of butadiene in mice and rats. Animals were exposed via inhalation at 0, 40, 200, and 1,000 ppm on gestation days 6-15 for 6 hours per day. No effects were seen in rats. A no-observed-adverse-effect level (NOAEL) of 200 ppm was identified for maternal toxicity in rats. In mice, reduced fetal weights were observed in all exposure levels with 40 ppm considered a

lowest-observed-adverse-effect level (LOAEL). Using a benchmark dose analysis, an LEC_{10} of 13.67 ppm was derived for reduction in mean fetal weight per litter. Using the LEC_{10}, the HPC was calculated as follows:

draft health protective concentration = LEC_{10} / UF = 13.67 / 100 = 0.14 ppm (140 ppb, rounded)

The cumulative uncertainty factor of 100 is based on a factor of 3.16 for extrapolation from a LOAEL to a NOAEL, 3.16 for interspecies differences, and 10 for interindividual differences. The factor of 3.16 represents the geometric mean between 1 and 10.

In comparison, applying an uncertainty factor to the observed LOAEL (instead of the LEC_{10} derived from the benchmark dose) gives a similar value as the benchmark dose calculation. In this case, the cumulative uncertainty factor is 300 based on a factor of 10 for extrapolation from the LOAEL to NOAEL, 3.16 for interspecies differences, and 10 for interindividual difference. A factor of 10 instead of 3.16 is used for extrapolation from the LOAEL to the NOAEL because use of the benchmark dose methodology reduces some of the uncertainty by utilizing the dose response curve to estimate a threshold for effects. Therefore, 40 ppm / 300 yields a value of 130 ppb (rounded).

Derivation of Proposed Chronic Reference Exposure Level

The proposed chronic REL is based on NTP (1993), which reported an increased incidence of ovarian atrophy in mice exposed to butadiene. In this study, mice were exposed to 0, 6.25, 20, 62.5, 200, or 625 ppm butadiene by inhalation 6 hours per day, 5 days per week for 103 weeks. The lowest exposure concentration (6.3 ppm) was identified as a LOAEL, while a NOAEL was not identified. Adjusting for the discontinuous exposure pattern, the average experimental concentration was calculated to be 1.1 ppm for the LOAEL group (6.3 ppm $\times$ 6/24 hours $\times$ 5/7days). An uncertainty factor of 300 was applied which incorporates uncertainty contributions for use of a LOAEL (10), interspecies scaling (3) and intraspecies scaling (10). Therefore, the proposed chronic REL is 4 ppb (0.004 ppm; 0.008 mg/m^3; 8 $\mu g/m^3$).

ETHANOL
CAS No.: 64-17-5

INTRODUCTION

Ethanol is formed by the fermentation of carbohydrates by various microorganisms. It is also produced synthetically from various petrochemical feedstocks, especially ethylene. The most quantitatively important source of human exposure to ethanol is consumption of alcoholic beverages. Due to the ubiquitous occurrence of microorganisms capable of ethanolic fermentation, virtually all sugar-containing foodstuffs are liable to contain a low level of ethanol. This is generally at the ppm level, or less than 1% by weight, except for materials deliberately fermented with an alcohol-tolerant strain of yeast. Ethanol is also a minor product of general metabolism in plants and animals, so a certain amount of endogenous exposure occurs even in the absence of external exposure. Information as to exposure actually occurring or anticipated as a result of the use of ethanol as a fuel additive is limited, in spite of the substantial use of ethanol in fuel in some areas of the U.S. and abroad.

KEY TOXICOLOGIC EFFECTS

Information in this section was primarily extracted from Clayton and Clayton (1994), ACGIH (1991) and Pastino et al. (1997). There is an enormous literature on the health effects of alcoholic beverages, which is of marginal relevance to the question at hand.

Acute Toxicity

At high vapor concentrations, ethanol is irritating to the eyes and the respiratory system. In humans, vapor concentrations above 40 mg/L (20,000 ppm) were considered intolerable. Similar concentrations caused sensory irritation in mice, evidenced by reduction in the breathing rate. Lester and Greenberg (1951) reported transient symptoms of respiratory and eye irritation in volunteers exposed to 10,000-20,000 mg/m^3 (5300 – 10,600 ppm) ethanol vapor. At 30,000 or 40,000 mg/m^3, more severe and continuing irritant responses were reported. They reported "no reaction" to 7500 mg/m^3 (3990 ppm) in patients being treated with tetraethylthiuram disulfide, a drug used to treat alcoholism by precipitating unpleasant symptoms on exposure to ethanol. (However, it is not clear whether the authors meant to include in this description no sensory irritation, or just none of the drug-related reactions to ethanol.) Based on these studies, and on case reports from industrial hygiene studies, OSHA, NIOSH and ACGIH regard 1000 ppm as a no-effect level for irritation (ACGIH, 1991). Ethanol appears to have little irritant effect on the skin.

Large oral or inhaled doses of ethanol cause narcosis, ataxia, and incoordination. These effects are observed in animals after exposure to 4,000 – 10,000 ppm for 8 hours. Humans reported headaches and other signs of incipient intoxication when exposed to levels in excess of about 3000 ppm for 2 hours. Hobbs et al. (1996) reported decreased reaction time, diminished fine motor coordination and impaired judgment after ethanol exposures resulting in blood alcohol concentrations of 4 – 7 mM.

At sufficiently high doses, death results from the effects of central nervous system depression. The oral LD_{50} for adult rats has been reported to range from 11.5 to 17.8 g/kg. Younger animals were more sensitive (LD_{50} = 6.2 g/kg). Inhalation of 10,000 – 30,000 ppm ethanol for extended periods (8 h or more) is lethal to rats. Consumption of large amounts of ethanol has also caused death in humans, but it appears to be difficult to approach the lethal dose level (>400 mg/dL in blood) by inhalation. Pastino et al. (1997) developed a physiologically based pharmacokinetic model for uptake of ethanol by inhalation in rats and mice, and extended this to the human situation by incorporation of appropriate measured parameters. The model was validated against the uptake data measured in humans by Lester and Greenberg (1951). They concluded that after exposure to 600 ppm ethanol, maximum blood ethanol concentrations were less than 10% of the concentration reported by Hobbs et al. (1996) as a threshold for behavioral effects.

Chronic Toxicity

Adverse effects on the liver have been noted in both animals and humans chronically exposed to ethanol. Symptoms initially include fatty infiltration and inflammation, and may progress to focal necrosis and/or fibrosis. Chronic oral doses to animals initiating these effects were typically 8 – 15 g/kg/day (rats, dogs). In humans these symptoms are well known, and are characterized as alcoholic hepatitis and cirrhosis. They are typically seen in abusers of alcoholic beverages. However, it is known that concurrent exposure to some other chemicals (such as carbon tetrachloride), and infection with hepatitis B virus, increase sensitivity to the liver damaging effects of ethanol.

In chronic abusers of alcoholic beverages, neurological and behavioral changes typical of peripheral and central nervous system damage are known. Some of the chronic neurological changes in alcohol abusers may be a result of altered patterns of nutrition.

Carcinogenicity

Ethanol has not been shown to be carcinogenic in laboratory animals, but acts as a promoter or co-carcinogen in animals concurrently exposed to other (carcinogenic) chemicals. For instance, long-term exposure to ethanol in drinking water promotes liver tumors in rats exposed to N-nitrosodiethylamine.

Heavy consumption of alcoholic beverages is known to be associated with increased incidences of some cancers, including those of the oral cavity, and of the liver (in subjects with evidence of advanced alcohol-related liver disease).

Ethanol is not genotoxic in most test systems, although a few equivocal or positive results have been reported, particularly in certain tests examining effects on chromosomes.

Reproductive and Developmental Toxicity

Rats and mice maintained on liquid diets containing 5 – 10% ethanol for 5 weeks or longer showed some adverse physical and functional effects on the testes. Some indications of toxicity

to the fetus, including deaths, growth retardation and increased malformations have been noted in rats and mice given diets in which 15-35% of the calories were derived from ethanol. However in other studies, no effect on the fetuses were seen in mice and rabbits given drinking water containing up to 15% ethanol, or inhaling up to 20,000 ppm ethanol, during pregnancy.

In humans, the "fetal alcohol syndrome" is a well-established consequence of maternal alcohol abuse during pregnancy. This includes retardation of growth and development, certain characteristic physical malformations, and also behavioral and cognitive problems. No reports have appeared of the occurrence of this syndrome after workplace exposures to ethanol by any route.

DOSE-RESPONSE ASSESSMENT

At this time, there are no health assessment values being used by California regulatory programs or by U.S. EPA for estimating potential health impacts from ethanol exposure through air or drinking water. Therefore, OEHHA calculated draft health protective concentrations (HPC) for the purposes of this report. In calculating the HPC for inhalation exposures, OEHHA followed the risk assessment methodology used for developing the acute reference exposure levels (RELs) under the Air Toxics Hot Spots Program risk assessment guidelines process (OEHHA, 1999a). As mandated by state legislation, these guidelines underwent scientific and public peer review, prior to approval by the Scientific Review Panel (Senate Bill 1731, Statutes of 1992, Ch. 1162 of the California Health and Safety Code). Due to the lack of scientific data on effects of extremely low level exposures to ethanol in water (and the probable lack of any such effects), a non-standard approach was taken in estimating a health protective concentration for ethanol in water.

Derivation of Health Protective Concentrations

Inhalation Exposures:

Lester and Greenberg (1951) reported inhalation exposures of volunteers to ethanol vapor, and reported transient (sensory) irritation effects, with a LOAEL of 5300 ppm (10,000 mg/m^3). It is unclear from the experimental account whether a NOAEL for irritant effects was established. The reported LOAEL is consistent with other human studies cited by ACGIH (1991). Since this effect appears from the data to be concentration dependent and does not represent a cumulative damage process, adjustment for duration of exposure is not appropriate. Although other chronic effects result at much higher exposure levels, the short-term LOAEL for irritation is expected to be protective from these also.

$$\text{draft health protective concentration} = \text{LOAEL/UF} = 53 \text{ ppm } (= 100 \text{ mg/m}^3).$$

The Uncertainty Factor (UF) used is 100, consisting of an intraspecies factor of 10 (reflecting the fact that the study population was selected to consist of healthy adult volunteers), and a LOAEL to NOAEL extrapolation factor of 10. Other factors are not required since the experimental level is determined in humans, and duration adjustments are not appropriate for the transient sensory response.

Drinking Water Exposures:

Predictions of ethanol dispersion and biodegradation in the environment indicate that ethanol is unlikely to occur in drinking water at levels having any toxicological significance. In particular, many beverages and food products naturally contain small amounts of ethanol, but are not required to report this provided that the content is less than 0.5%. This level is probably not selected for health-protective reasons alone, but nevertheless appears a reasonable basis for identifying a level with no important biological effects in the majority of the population. In setting an upper limit for water, it is necessary take into account ethanol from other sources like food. It seems unlikely that 100% of the 1.5 kg diet would contain 0.5% ethanol. For the present estimate, it was assumed 0.5 kg of the diet might contain ethanol at 0.5%, and that it is undesirable for water to contribute more than this amount. Furthermore, assuming a direct water consumption of 2 L/d, and a 10% additional contribution by inhalation of ethanol from tap water (e.g., during showering, dish washing, etc.), a draft health protective concentration in water can be calculated as follows:

draft health protective concentration = 0.5% x 0.5 kg/d / 2.2 Leq/d = 0.11% (1,100 ppm)

Although based on the reporting level for foods and beverages, this allows less ethanol in water than in food products, recognizing that exposure to water can be greater, and involves other routes of exposure, albeit to limited degrees.

FORMALDEHYDE
CAS No: 50-00-0

INTRODUCTION

Formaldehyde is both directly emitted into the atmosphere and formed in the atmosphere as a result of photochemical oxidation of reactive organic gases in polluted atmospheres containing ozone and nitrogen oxides. Photochemical oxidation is the largest source (could be as high as 88%) of formaldehyde concentrations in California ambient air. A primary source of formaldehyde is vehicular exhaust (CARB, 1992; U.S. EPA, 1993). Formaldehyde is a product of incomplete combustion. About 9% of direct formaldehyde emissions are estimated to come from the combustion of fossil fuels from mobile sources (Lawson et al., 1990). Formaldehyde is routinely monitored by the statewide California Air Resources Board (CARB) toxics monitoring network. The mean concentration of formaldehyde from January 1994 through December 1994 monitored by the CARB network was estimated to be 2.66 micrograms per cubic meter ($\mu g/m^3$) or 2.1 ppb (CARB, 1995). When formaldehyde was formally identified as a Toxic Air Contaminant (TAC) the CARB estimated a population-weighted annual concentration of 5.4 $\mu g/m^3$ or 4.4 ppb (CARB, 1992).

KEY TOXICOLOGIC EFFECTS

Acute Toxicity

Exposure to moderate levels of formaldehyde (1-3 ppm) can result in eye and upper respiratory tract irritation (Weber-Tschopp et al., 1977; Kulle et al., 1987). Feinman (1988) states that most people cannot tolerate exposures to more than 5 ppm formaldehyde in air; above 10-20 ppm symptoms become severe and shortness of breath occurs. High concentrations of formaldehyde may result in nasal obstruction, pulmonary edema, choking, dyspnea, and chest tightness (Porter, 1975; Solomons and Cochrane, 1984). Rhinitis and a wide range of asthma-like conditions can result from exposure to formaldehyde. Some studies have reported that workers exposed to low concentrations may develop severe prolonged asthma attacks after prior exposure (Feinman, 1988).

Chronic Toxicity

Formaldehyde primarily affects the mucous membranes of the upper airways and eyes; these effects include potentially precancerous nasal epithelial histological lesions, including keratosis and metaplasia of the nasal epithelium (Edling et al., 1988). Repeated exposure of skin to the liquid also causes irritation and allergic dermatitis.

Dose-dependent increases in health complaints (eye and throat irritation, and headaches) have been noted in residents of mobile and conventional homes at concentrations of 0.1 ppm formaldehyde or above (Ritchie and Lehnen, 1987). Similarly, Liu et al. (1991) found that exposure to 0.09 ppm (0.135 mg/m^3) formaldehyde exacerbated chronic respiratory and allergy problems in residents living in mobile homes. Chronic exposure to formaldehyde has been

associated with immunological hypersensitivity and altered immunity (Thrasher et al., 1987). Thrasher et al. (1990) later found that long-term exposure to formaldehyde was associated with autoantibodies, immune activation, and formaldehyde-albumin adducts. The authors suggest that the hypersensitivity induced by formaldehyde may account for a mechanism for asthma and other health complaints associated with formaldehyde exposure.

Carcinogenicity

Epidemiological studies have shown formaldehyde exposure to be significantly associated with cancer at sites in the respiratory tract in workers and in the general population (OEHHA, 1992a). Studies of embalmers, who have used formaldehyde, have shown increased rates of brain cancer and of leukemia. Formaldehyde is carcinogenic in rodents, producing squamous cell carcinomas in the nasal passages of male and female rats and male mice. Both the International Agency for Research on Cancer and the U.S. EPA have classified formaldehyde as a probable human carcinogen, based on sufficient evidence for carcinogenicity in animals and limited evidence in humans. OEHHA (1992a) developed a cancer unit risk factor for formaldehyde of 6.0×10^{-6} $(\mu g/m^3)^{-1}$ based on rat nasal tumor data (Kerns et al., 1983).

Reproductive and Developmental Toxicity

Exposure of experimental animals to formaldehyde does not appear to result in any significant teratogenic or reproductive effects (CARB, 1992). Formaldehyde is not listed by the State of California as a reproductive or developmental toxicant under Proposition 65, California's Safe Drinking Water and Toxic Enforcement Act of 1986.

DOSE-RESPONSE ASSESSMENT

The following table contains available health assessment values for formaldehyde currently used by California regulatory programs.

Table 4. Health assessment values for formaldehyde

	Health Assessment Value	Reference
Acute reference exposure level (REL)	94 $\mu g/m^3$	OEHHA (1999a)
Proposed chronic reference exposure level (REL)	3 $\mu g/m^3$	OEHHA (1999c)
Cancer potency factor	2.1×10^{-2} $(mg/kg\text{-}day)^{-1}$	OEHHA (1999b)
Unit risk factor	6.0×10^{-6} $(\mu g/m^3)^{-1}$	OEHHA (1999b)
No significant risk level (NSRL)	40 µg/day	OEHHA (1994b)
U.S. EPA reference dose (RfD)	2×10^{-1} (mg/kg-day)	U.S. EPA (1990)
U.S. EPA reference concentration (RfC)	NA	---
Public health goal (PHG)	NA	---
U.S. EPA Lifetime Health Advisory for drinking water (based on 70 kg adult)	1 mg/L	U.S. EPA (1996)

NA = not available

Since adopted health assessment values suitable for assessing chronic inhalation exposures are not available for formaldehyde, OEHHA has selected the proposed chronic reference exposure level (REL) for use in this report. The proposed chronic REL is currently being developed under the Air Toxics Hot Spots Program risk assessment guidelines process (Senate Bill 1731, Statutes of 1992, Ch. 1162 of the California Health and Safety Code). The methodology used to derived the proposed chronic REL for formaldehyde, as well as the number itself, have undergone an initial round of public and scientific peer review, and is currently being considered by the State's Scientific Review Panel (1999c). The derivation of the proposed chronic REL is summarized below, and explained in detail in OEHHA (1999c).

Derivation of Proposed Chronic Reference Exposure Level

Occupational exposure of 66 workers to formaldehyde for 1 - 36 years (mean = 10 years) resulted in significantly increased symptoms of irritation including nasal and eye irritation, and lower airway discomfort (Wilhelmsson and Holmstrom, 1992). The workers were exposed to a mean concentration of 0.17 ppm while the control group was exposed to a mean concentration of 0.06 ppm. The increase in symptoms of irritation in exposed workers did not correlate with total serum IgE antibody levels. This study is supported by the results of Horvath et al. (1988) which observed significant differences in subjective irritation and pulmonary function in 109 workers exposed to formaldehyde compared to 254 control subjects. The mean formaldehyde concentrations for the exposed and control groups were 0.69 ppm and 0.05 ppm, respectively. Duration of formaldehyde exposure was not stated.

The study by Wilhelmsson and Holmstrom (1992) establishes a NOAEL of 0.06 ppm for long-term irritant effects in humans. Following adjustment of the NOAEL for exposure continuity (10 m^3/day occupational exposure / 20 m^3/day total exposure, 5/7 days per week), the average occupational concentration is 0.02 ppm.

$$\text{Proposed chronic REL} = \text{NOAEL} / \text{UF} = 0.02 / 10 = 0.002 \text{ ppm } (= 0.003 \text{ mg/m}^3)$$

An uncertainty factor (UF) of 10 was applied, based only upon an intraspecies factor of 10, reflecting the fact that the study population consisted of healthy adult workers. Other factors are not required since the experimental level is determined in humans.

HEXANE
n-Hexane, CAS No.: 110-54-3

INTRODUCTION

Hexane, derived by the distillation and catalytic cracking of crude oil, is an important constituent of gasoline and light petroleum solvents such as petroleum ether. It is also used as a cleaning agent, in glues and paint thinner, and in the solvent extraction of soybean and other food oils. Several different hexane isomers are found in these products; this discussion mainly concerns the unbranched isomer, n-hexane.

The very high volatility, low water solubility, and relatively low soil binding of hexane result in rapid equilibration into the vapor phase after environmental contamination. It does not absorb UV light, so photolysis is expected to be unimportant. Reaction with hydroxyl radical is probably the most important degradation pathway in air (HSDB, 1998). Hexane can also be rapidly degraded by microbes in soil or sewage sludge, but will persist longer in high-concentration hydrocarbon phases in soil. It does not bioconcentrate in sediment, plants, or animals.

Hexane is emitted into the atmosphere from gasoline evaporation and as a constituent of the unburned hydrocarbon fraction in tailpipe emissions. It also is released by evaporation of common solvents and drying of oil-based paints; it is also a product of plant metabolism. Levels of hexane in the low ppb range are commonly detected in both urban and rural atmosphere. Around refineries, manufacturing plants, or hazardous waste sites, concentrations in air approaching 50 ppm have been measured (HSDB, 1998). Hexane is not commonly detected in drinking water, but may be found at trace levels in ground or surface water as a result of natural processes or industrial emissions.

KEY TOXICOLOGIC EFFECTS

Acute Toxicity

Hexane has relatively low acute toxicity. Inhalation, the usual exposure route, may result in some eye, nose, and respiratory tract irritation at concentrations in air above about 1000 ppm. Mild excitation may occur at low doses (disinhibition), followed by sedation and narcosis at higher concentrations and prolonged exposures (usually greater than 5000 ppm). Hepatotoxicity may also occur after acute high doses.

Chronic Toxicity

The primary consideration in chronic exposures to n-hexane is neurotoxicity, which has been observed in animal studies and in human occupational exposures. The toxicity is caused by metabolism of the hexane to 2,5-hexanedione, which apparently crosslinks structural or transport proteins in nerve axons (Lapadula et al., 1986). This results in a peripheral dying-back axonopathy associated with tingling and weakness in the limbs, which may progress to limb

paralysis (Sobue et al., 1978; O'Donoghue, 1985; U.S. EPA, 1999c). Branched-chain hexane isomers do not form metabolites that react similarly to 2,5-hexanedione, and these isomers therefore have minimal or no potential to cause the classical hexacarbon neuropathy.

Peripheral neuropathy has been clearly observed in rats with subchronic exposures to about 1000 ppm for 8 hours per day, 5 days per week (Rebert et al., 1982); more subtle changes may be observed in rodents at levels of a few hundred ppm (HSDB, 1998). Human neurotoxic effects are clear at estimated occupational concentrations of 100 ppm or more, and appear likely at chronic exposure levels in excess of 50 ppm (Iida, 1982; Sanagi et al., 1980; Wang et al., 1986).

Carcinogenicity

There are apparently no applicable studies on carcinogenicity of n-hexane. Hexane is not mutagenic in Ames assays nor genotoxic in a variety of short-term tests. However, an increased frequency of chromosomal aberrations was observed in rat bone marrow cells after exposures to concentrations as low as 100 ppm, 6 hours per day for 5 days to 4 weeks (Hazleton, 1980).

Reproductive and Developmental Toxicity

Teratogenicity tests in rats and rabbits show no specific malformations, even at maternally toxic doses. Testicular toxicity is noted in male rats with prolonged exposures to hexane at concentrations of about 1000 ppm or more (Nylen et al., 1989).

DOSE-RESPONSE ASSESSMENT

The following table contains available health assessment values used by California regulatory programs for hexane.

Table 5. Health assessment values for n-hexane.

	Health Assessment Value	Reference
Acute reference exposure level (REL)	NA	---
Cancer potency factor	NA	---
Unit risk factor	NA	---
No significant risk level (NSRL)	NA	---
U.S. EPA reference dose (RfD)	NA	---
U.S. EPA reference concentration (RfC)	0.2 mg/m^3	U.S. EPA (1999c)
Public health goal (PHG)	NA	---

NA = not available

ISOBUTENE
CAS No.: 115-11-7

INTRODUCTION

Isobutene is a chemical intermediate (butyl rubber production, plastics, adhesives), and a component of unleaded gasoline. Only a few isobutene toxicity studies have been reported. However, the studies available indicate that isobutene is probably mutagenic. A long term study demonstrated possible carcinogenic effects, but the data fell short of the criteria for sufficient evidence of carcinogenicity.

KEY TOXICOLOGIC EFFECTS

Acute Toxicity

Shugaev and Yaroslavl (1969) reported a 2-hour LC_{50} (concentration lethal to one-half of the animals exposed) in mice of 178,000 ppm; the same study reported a 4-hour LC_{50} in rats of 266,000 ppm.

Chronic Toxicity

No toxicity was noted in male and female rats exposed to isobutene by gavage for 4 weeks at concentrations of 2, 15 or 149 mg/kg-day (BG Chemie, 1989; reviewed by Cornet and Rogiers, 1997). No significant evidence of toxicity was observed in male and female rats exposed to isobutene by inhalation at concentrations of 250, 1000 or 8000 ppm for 13 weeks (BG Chemie, 1989; reviewed by Cornet and Rogiers, 1997).

Groups of 50 male and 50 female F344/N rats and $B6C3F_1$ mice were exposed to isobutene at concentrations of 0, 500, 2,000, or 8,000 ppm 6 hours per day, 5 days per week, for 105 weeks (NTP, 1998). Survival of exposed male and female rats and mice was similar to that of the chamber controls. Mean body weights of exposed rats were generally similar to those of the chamber controls throughout the study. Mean body weights of exposed mice were generally similar to those of the chamber controls throughout the study except for female mice exposed to 2,000 or 8,000 ppm, which weighed slightly less than chamber controls from about week 52 until week 92. The incidences of hyaline degeneration of the olfactory epithelium were marginally increased in exposed rats; however, the severity of hyaline degeneration increased with increasing exposure concentration in both males and females. The incidences of hyaline degeneration of the respiratory epithelium in all groups of exposed male and female mice were significantly greater than those in the chamber control groups. The incidences of hyaline degeneration of the olfactory epithelium in 2,000 and 8,000 ppm mice were greater than those in the chamber controls.

Carcinogenicity

Isobutene genotoxicity data are mixed. Negative results with isobutene have been reported in several strains of *Salmonella typhimurium* (Staab and Sarginson, 1984; Shimizu et al., 1985; Cornet et al., 1992; NTP, 1998) and in L5178Y mouse lymphoma cells (Staab and Sarginson, 1984), with and without rat liver S9 metabolic activation. Additionally, no induction of micronuclei in human lymphocytes exposed to isobutene *in vitro* were noted by Jorritsma *et al.* (1995). The studies by Cornet *et al*. (1992), Jorritsma *et al.* (1995) and NTP (1998) specifically used testing protocols designed to account for isobutene volatility. However, positive results were reported for gene mutation in S. *typhimurium* (Cornet et al., 1992; Castelain et al., 1993) and *Klebsiella pneumoniae* (Voogd et al., 1981) as well as chromosome damage in lymphocytes (Jorritsma et al., 1995) when the primary metabolite of isobutene, 2-methyl-1,2-epoxypropane, was tested in the absence of metabolic activation enzymes.

Groups of 50 male and 50 female F344/N rats and B6C3F_1 mice were exposed to isobutene at concentrations of 0, 500, 2,000, or 8,000 ppm 6 hours per day, 5 days per week, for 105 weeks (NTP, 1998). No increases in tumor incidences were noted in female rats or male and female mice. However, the incidence of thyroid gland follicular cell carcinomas in male rats exposed to 8,000 ppm was increased (although not significantly) compared to the chamber control group and exceeded the historical control range. The thyroid gland follicular cell carcinoma incidences in male rats in the 0, 500, 2,000 and 8,000 ppm exposure groups were 1/48, 0/48, 0/48 and 5/50, respectively.

Reproductive and Developmental Toxicity

No studies on isobutene reproductive or developmental toxicity have been reported in the open literature.

DOSE-RESPONSE ASSESSMENT

At this time, there are no health assessment values being used by California regulatory programs or by U.S. EPA for estimating the potential health impacts from isobutene. Since adopted health assessment values are not available, OEHHA calculated a draft health protective concentration (HPC) for the purpose of this report. In calculating the HPC, OEHHA followed the risk assessment methodology being used to develop the chronic reference exposure levels (RELs) under the Air Toxics Hot Spots Program risk assessment guidelines process. As mandated by state legislation, these guidelines must undergo scientific and public peer review prior to approval by the Scientific Review Panel (Senate Bill 1731, Statutes of 1992, Ch. 1162 of the California Health and Safety Code). While the chronic REL methodology has not been adopted at this time, it has undergone an initial round of public and scientific peer review, and is currently being considered by the Panel. The derivation of the HPC for chronic inhalation exposures is summarized below. Further details on the methodology are provided in OEHHA (1999c). The available toxicity data were insufficient to allow the calculation of an acute HPC or cancer unit risk HPC for isobutene.

Derivation of Health Protective Concentration

NTP (1998) found that isobutene caused significantly increased incidences of respiratory epithelium hyaline degeneration in male and female $B6C3F_1$ mice exposed to 500, 2000 and 8000 ppm when compared to chamber control group animals. A lowest-observed-adverse-effect level (LOAEL) of 500 ppm was observed; a no-observed-adverse-effect level (NOAEL) was not observed in this study. A chronic draft HPC can be calculated for isobutene using the formula:

$$\text{draft health protective concentration} = \text{LOAEL} / \text{UF} = 2.6\ \text{mg/m}^3\ (1.1\ \text{ppm})$$

The uncertainty factor (UF) for this calculation is 450, which incorporates uncertainty contributions for extrapolation from a "mild effect" LOAEL to a NOAEL (factor of 3), extrapolation from animals to humans using U.S. EPA HEC methodology (U.S. EPA, 1994a) (factor of 15) and for potentially sensitive human subpopulations (10). The animal to human extrapolation factor of 15 was calculated by multiplying a dosimetric adjustment of 5 (using default body weights of 0.0353 and 70 kg for female mice and humans, respectively, and respiratory tract surface area values of 3 and 200 cm^2 for female mice and humans, respectively) by a default uncertainty factor of 3, which is meant to compensate for potential animal-human differences not accounted for by dosimetry.

METHYL TERTIARY BUTYL ETHER (MTBE)

CAS No.: 1634-04-4

INTRODUCTION

Reformulated gasoline containing up to 11% MTBE has been widely used in California since 1996. MTBE is present in ambient air in California, at a statewide average of approximately 2 ppbv, with higher average concentrations in urban areas (e.g., 4 ppbv in the South Coast region), as of March, 1999 (OEHHA, 1999f). Sources of MTBE in ambient air include the manufacture and distribution of oxygenated gasoline, vehicle refueling, and evaporative and tailpipe emissions from motor vehicles.

Due to high water solubility, lack of binding to soil, and persistence in solution, MTBE has become a drinking water contaminant in California. MTBE has been detected in numerous drinking water wells and surface water sources within the state, in addition to multiple detections in groundwater. Sources of MTBE in drinking water include leaking underground storage fuel tanks, recreational power-boating, and refinery wastewater.

Individuals may be exposed to MTBE in contaminated air and water via inhalation, ingestion, and dermal absorption.

KEY TOXICOLOGIC EFFECTS

Acute Toxicity

A number of non-specific acute symptoms have been reported following MTBE exposure, including noticeable odor, headache, nausea or vomiting, burning sensation in the nose or mouth, cough, dizziness, disorientation and eye irritation (University of California, 1998). The existing epidemiological studies of the acute effects of MTBE exposure have reported inconsistent results; however, each of the studies had methodological limitations. There is a need to conduct additional studies specifically designed to identify and characterize the acute human health effects associated with MTBE exposure.

Studies in animals have demonstrated the low toxicity of MTBE, with an acute inhalation NOAEL of 1,440 mg/m^3 and an acute oral NOAEL of 40 mg/kg-day (OEHHA, 1999f). Acute effects of MTBE exposure in animals include profound, but reversible general anesthetic effects, decreased breathing rates, and irritation to the nasal mucosa and gastrointestinal tract (OEHHA, 1999f).

Chronic Toxicity

There are presently no human data on the chronic health effects of MTBE exposure. In rats, effects observed include increased relative organ weights for kidney, liver and adrenal gland, increased hyaline droplets in male kidneys, elevated cholesterol, and dysplastic proliferation of lymphoreticular tissues in females (OEHHA, 1999f).

Carcinogenicity

There are no human data on which an evaluation of the carcinogenicity of MTBE can be based. However, there is substantial evidence that MTBE administered by either the oral or inhalation routes is carcinogenic in rats and mice. MTBE causes leukemias and lymphomas in female rats by the oral route, Leydig interstitial cell tumors of the testes in male rats by the oral and inhalation routes, renal tubular tumors in male rats by the inhalation route, and hepatocellular tumors in mice of both sexes by the inhalation route (OEHHA, 1998a). Based on a thorough review of the relevant data, including supporting data on pathology and mechanisms of tumor induction, and carcinogenicity studies of MTBE's primary metabolites TBA and formaldehyde, the UC Report concluded that MTBE is an animal carcinogen with the potential to cause cancer in humans (University of California, 1998). IARC recently classified MTBE as a Group 3 carcinogen (i.e., not classifiable as to carcinogenicity in humans), based on inadequate evidence in humans and limited evidence in experimental animals (IARC, *in press*, cited in OEHHA, 1999f).

Reproductive and Developmental Toxicity

There are no human data on which an evaluation of the developmental or reproductive toxicity of MTBE can be based. Studies in animals suggest that MTBE has the potential to cause developmental toxicity, based on reports of developmental retardation in rats (i.e., postnatal growth retardation) and mice (i.e., lower fetal weights at term, reduced skeletal ossification) (OEHHA, 1998b). MTBE exposure did not result in any observable effects on female fertility in two reproductive toxicity studies in the rat, the only species tested to date. Observations of lower relative uterine and ovarian weights and lengthened estrous cycles in female mice suggest that MTBE may have antiestrogenic effects, however. There are very limited data available from animal studies on the potential for MTBE to cause male reproductive toxicity. No adverse effects on male fertility or reproductive organ weights have been reported, although one study found lower levels of plasma testosterone in rats exposed to MTBE (OEHHA, 1998b).

DOSE-RESPONSE ASSESSMENT

The following table contains available health assessment values used by California regulatory programs for MTBE.

Table 6. Health assessment values for MTBE

	Health Assessment Value	Reference
Acute reference exposure level (REL)	NA	---
Proposed chronic reference exposure level	3 mg/m^3	OEHHA (1999c)
Cancer potency factor	1.8×10^{-3} $(mg/kg\text{-}day)^{-1}$	OEHHA (1999f)
Unit risk factor	2.6×10^{-7} $(\mu g/m^3)^{-1}$	OEHHA (1999f)
No significant risk level (NSRL)	Not listed under P65	---
Drinking Water Advisory	20-40 ppb	U.S. EPA (1997b)
U.S. EPA reference dose (RfD)	NA	---
U.S. EPA reference concentration (RfC)	3 mg/m^3	U.S. EPA (1997c)
Public health goal	13 ppb	OEHHA (1999f)

NA = not available

Since adopted health assessment values suitable for assessing potential health impacts from short-term inhalation exposures to MTBE are not available, OEHHA calculated a draft health protective concentration (HPC) for the purpose of this report. In calculating the HPC, OEHHA followed the risk assessment methodology used for developing the acute reference exposure levels (RELs) under the Air Toxics Hot Spots Program risk assessment guidelines process (1999a). As mandated by state legislation, these guidelines underwent scientific and public peer review, prior to approval by the Scientific Review Panel (Senate Bill 1731, Statutes of 1992, Ch. 1162 of the California Health and Safety Code) and adoption by OEHHA. The derivation of the HPC is summarized below. Further details on the methodology are provided in OEHHA (1999a).

Derivation of Health Protective Concentration

In two-hour chamber studies in which humans were exposed to MTBE during light exercise, Nihlen *et al*. (1998) reported no toxic effects at exposure levels up to 50 ppm MTBE. Endpoints of interest in the study were irritative symptoms, discomfort, and CNS effects. Upon entry into the chamber, subjects reported a 'solvent smell' which gradually declined. Odor detection at this level of exposure is consistent with that reported in other studies (University of California, 1998). This study establishes a NOAEL of 50 ppm for irritative effects in humans for a 2 hour exposure. Applying a modified "Haber's Law" calculation to extrapolate from 2 hours to 1 hour, the equivalent NOAEL is 70 ppm for irritative effects.

$$C^nT = K$$
$$C^n{}_1T_1 = C^n{}_2T_2 \text{ where n=2 based on extrapolation from 120 min. to 60 min.}$$
$$C^2\,(60) = (50\text{ ppm})^2\,(120\text{ minutes})$$
$$C = 70\text{ ppm}$$

Using the adjusted NOAEL, a draft HPC can be calculated as follows:

draft health protective concentration = NOAEL / UF = 70 / 10 = 7 ppm (25 mg/m^3)

An uncertainty factor (UF) of 10 was applied, based only upon an intraspecies factor of 10, reflecting the fact that the study population consisted of healthy adult volunteers. Other factors are not required since the experimental level is determined in humans and duration adjustments are not appropriate for the transient sensory response.

PEROXYACETYL NITRATE (PAN)
CAS No.: 2278-22-0

INTRODUCTION

Peroxyacetyl nitrate (PAN) is one of a class of common air pollutants, peroxyacyl nitrates, formed by photochemical oxidation from volatile organic hydrocarbons and nitrogen dioxide. PAN acts as a storage reservoir for nitrogen oxides (NO_x) and can accelerate photochemical smog formation. PAN may also contribute to ozone formation downwind of urban areas by transporting NO_x. It is now recognized that PAN is of major importance (along with ozone) when evaluating air quality. PAN concentrations were measured at various ground sites and aloft on three occasions during the summer and fall of 1987 as part of the Southern California Air Quality Study (SCAQS) (CARB, 1989). Urban PAN concentrations in the South Coast Air Basin ranged from 1.1 to 30 ppb. Measurements of PAN in non-air conditioned rooms have shown maximal indoor concentrations of close to 100% of the corresponding outdoor concentrations, with average indoor/outdoor concentration ratios ranging between 0.7 and 0.9 (Jakobi and Fabian, 1997).

KEY TOXICOLOGIC EFFECTS

Acute Toxicity

PAN has been demonstrated to cause eye irritation in humans. A PAN concentration of 4.95 mg/m^3 caused significant eye irritation in 20 human volunteers in 10-15 minutes (Stephens et al., 1961). Drechsler-Parks (1987) found that PAN induced eye irritation in subjects at a concentration of 0.64 mg/m^3 (0.13 ppm).

Human studies examining the effects of PAN on the respiratory system produced varied results. Several studies reported no effect of PAN alone or in the presence of ozone and/or nitrogen dioxide on respiratory functions during exercise of duration ranging from 42 minutes to 2 hours, and at concentrations ranging from 0.64 to 1.49 mg/m^3 (Raven et al., 1974a; Raven et al., 1974b; Drechsler-Parks et al., 1984; Drechsler-Parks, 1987; Drechsler-Parks et al., 1987; Drechsler-Parks et al., 1989; Horvath et al., 1986).

Smith (1965) found that young males exposed to a PAN concentration of 1.49 mg/m^3 during 5 minutes of light exercise did not result in any change in respiratory rate or expiratory volume compared to exercise in clean air. However, oxygen requirements were increased in the presence of PAN. The authors suggested that this was the result of an increase in respiratory airway tissue resistance. A small but statistically significant reduction (4%) in forced vital capacity (FVC) was observed in young males (mean age = 23) performing light exercise while exposed to 1.19 mg/m^3 PAN for 4 hours (Raven et al., 1976). However, no changes were noted in mean inspiratory capacity, expiratory reserve volume or forced expiratory volume over 1 second ($FEV_{1.0}$). Additionally, older subjects (mean age = 48) exposed to PAN under the same conditions did not show changes in FVC.

As part of the Houston area longitudinal epidemiological oxidant study, Javitz et al. (1982) reported a greater incidence of subjective symptoms in 286 subjects with chronic obstructive pulmonary disease (COPD) exposed to ambient concentrations of PAN up to 0.059 mg/m^3. Logistic regressions of a selected set of self-reported health symptoms on oxidants indicated that the incidence of chest discomfort and eye irritation increased by 10.1% and 7.5%, respectively, as PAN increased from 0 to 0.059 mg/m^3.

An LC_{50} (concentration producing mortality in 50% of the animals exposed) for a 2-hour exposure to PAN in strain A male mice for 9 week old and 15 week old animals was reported as being 718-743 mg/m^3 and 495-545 mg/m^3, respectively (Campbell et al., 1967). Kruysse et al. (1977) reported a 4-hour LC_{50} for PAN in 9-week old male and female Wistar rats of 470 mg/m^3 (95 ppm).

A significant increase in mortality due to acute respiratory pneumonia caused by inhalation of *Streptococcus pyogenes* aerosol was seen after a single 3-hour exposure of mice to 14.8-28.4 mg/m^3 PAN (Thomas et al., 1981). The excess mortality ranged from 8 to 39% and the decrease in survival time ranged from 2.4 to 7.9 days.

Chronic Toxicity

Kruysse et al. (1977) exposed male and female Wistar rats to PAN for 6 hours/day, 5 days/week for either 4 or 13 weeks. PAN concentrations used in the 4 week study were 0, 0.9, 4.1, or 11.8 ppm; concentrations used in the 13 week study were 0, 0.2, 1.0 or 4.6 ppm. In the 4 week study, exposure to 11.8 ppm caused elevated mortality, hematocrit values, red blood cell counts and lung weight, abnormal behavior, growth retardation, and severe inflammation and epithelial metaplasia and hyperplasia in the respiratory tract. Minimal behavioral disturbance, transient growth retardation, slightly increased lung weights and slight histopathological changes in the respiratory tract were noted at 4.1 ppm. No treatment related effects were noted at 0.9 ppm. Exposure to 4.6 ppm in the 13 week study resulted in changes similar to those found at 11.8 ppm in the 4 week study, with the exception that elevated mortality was not observed. No treatment-related effects exhibiting a dose-response were observed at 1.0 ppm.

Male strain A mice were exposed by Dungworth et al. (1969) to 74.3 mg/m^3 (15 ppm) PAN for 6 hours/day, 5 days/week for 6 months. Toxic effects noted included hyperplastic tracheobronchitis, bronchiolitis, pneumonitis, bronchiolectasis, bronchiolarization of alveolar ducts, a focal interstitial fibrotic reaction and patchy centriacinar emphysema. Hyperplasia of the bronchial epithelium was also observed, and foci of squamous metaplasia were observed in the trachea and mainstem bronchi in approximately 50% of the PAN-exposed mice. The authors did not interpret these foci as being neoplastic, but did consider them potentially precancerous.

Carcinogenicity

No human or animal carcinogenicity data exist for PAN. As described above, Dungworth et al. (1969) did note foci of squamous metaplasia in the trachea and mainstem bronchi in PAN-exposed mice, and evaluated those foci as being potentially precancerous but not neoplastic as observed.

Genotoxicity data for PAN is mixed. Kleindienst et al. (1990) found that PAN induced mutations in *Salmonella typhimurium* strain TA100 in the absence of exogenous metabolic activation. Kligerman et al.(1995) reported that an increase in DNA damage was noted in the single cell gel (SCG) in mouse peripheral blood lymphocytes (PBLs) exposed to PAN *in vitro* at concentrations that were cytotoxic (inhibited cell division). However, at lower exposure levels that permitted cell division, no increases in sister chromatid exchanges (SCEs), chromosomal aberrations (CAs), or DNA damage were evident. Male mice were exposed nose-only by inhalation for 1 hour to 0, 15, 39 or 78 ppm PAN, and their lung cells removed and cultured for the scoring of SCEs and CAs. In addition, PBLs and lung cells were analyzed by the SCG assay. No dose-related effects were found in any of the assays. Chinese hamsters exposed to PAN concentrations of approximately 3 ppm for up to 1 month did not show significantly increased frequencies of either gene mutations in lung fibroblasts or increased micronuclei frequency indicating CAs in either lung fibroblasts or red blood cells.

Reproductive and Developmental Toxicity

No reproductive or developmental toxicity studies on PAN have been reported in the open literature.

DOSE-RESPONSE ASSESSMENT

At this time, there are no health assessment values being used by California regulatory programs or by U.S. EPA for estimating potential health impacts from PAN. Since adopted values are not available, OEHHA calculated draft health protective concentrations (HPCs) for the purpose of this report. In calculating the short-term HPCs, OEHHA followed the risk assessment methodology adopted for use in developing acute reference exposure levels (RELs) under the Air Toxics Hot Spots Program risk assessment guidelines process. As mandated by state legislation, these guidelines underwent scientific and public peer review, prior to approval by the Scientific Review Panel (Senate Bill 1731, Statutes of 1992, Ch. 1162 of the California Health and Safety Code) and adoption by OEHHA. A detailed description of the methodology is provided in OEHHA (1999a). In addition, in the absence of an adopted health assessment value suitable for assessing chronic inhalation exposures, OEHHA followed the methodology being used to develop chronic RELs, also legislatively mandated Air Toxics Hot Spots Program risk assessment guidelines process. While the chronic REL methodology has not been adopted at this time, it has undergone an initial round of public and scientific peer review, and is currently being considered by the State's Scientific Review Panel (1999c). The derivation of the draft HPCs are summarized below.

Derivation of Health Protective Concentrations

The short-term HPC is based on Drechsler-Parks (1987) who found that a 2-hour exposure to PAN induced eye irritation in male and female human volunteers at a concentration of 0.64 mg/m^3 (0.13 ppm). This concentration was a lowest-observed-adverse-effect level (LOAEL); a no-observed-adverse-effect level (NOAEL) was not observed in this study. After

applying a modification of "Haber's Law" to extrapolate from a 2-hour to a 1-hour exposure duration, the LOAEL is 0.18 ppm.

$$C^nT = K$$
$$C^n_1T_1 = C^n_2T_2 \text{ where n=2 based on extrapolation from 120 min. to 60 min.}$$
$$(0.13 \text{ ppm})^2 (120) = C^2 (60)$$
$$C = 0.18 \text{ ppm}$$

A cumulative uncertainty factor (UF) of 100 is applied based on a factor of 10 to account for extrapolation from a LOAEL to a NOAEL and 10 to account for intraspecies variability. Therefore, an acute 1-hour HPC can be calculated for PAN as follows:

draft health protective concentration = LOAEL / UF = 1.8 ppb (8.8 $\mu g/m^3$)

The HPC for chronic exposures is based on Kruysse et al. (1977), who exposed male and female Wistar rats to PAN concentrations of 0, 0.2, 1.0 or 4.6 ppm for 6.5 hours per day, 5 days per week for 13 weeks. Exposure to 4.6 ppm caused elevated hematocrit values, decreased lymphocyte counts, increased lung weights, abnormal behavior, growth retardation, and inflammation, epithelial metaplasia and hyperplasia in the respiratory tract. No treatment-related effects exhibiting a dose-response were observed at 1.0 ppm. The NOAEL identified in this study was 1.0 ppm (4.95 mg/m^3), based on respiratory tract toxicity observed at the next highest dose, 4.6 ppm. An equivalent time-weighted average concentration (C_{AVG}) was calculated from the observed concentration (C_{OBS}) using the relationship:

$$C_{AVG} = 4.95 \text{ mg/m}^3 \times (6.5 \text{ hr}/24 \text{ hr}) \times (5 \text{ days}/7 \text{ days}) = 0.96 \text{ mg/m}^3$$

A draft HPC for chronic exposures can be calculated for PAN using the formula:

draft health protective concentration = NOAEL / UF = 3.2 $\mu g/m^3$ (0.6 ppb)

The uncertainty factor (UF) used is 300, and is derived by multiplying a UF of 10 for interspecies variation by a UF of 10 for intraspecies variability and a UF of 3 for subchronic to chronic time extrapolation.

TERTIARY BUTYL ALCOHOL (t-Butanol)
CAS No.: 75-65-0

INTRODUCTION

Tertiary butyl alcohol (TBA) has been used as a gasoline octane booster and may be a food contaminant when used in coatings for metallic items that contact food, or as a coating for paperboard food containers. Human exposure can occur via skin contact, inhalation, or ingestion. The Occupational Safety and Health Administration has established a permissible exposure limit of 100 ppm or 300 mg/m^3 for TBA for workplace exposures. TBA is partially metabolized via demethylation in rats to acetone and formaldehyde. TBA is a metabolite of MTBE and exposure may occur through inhalation of MTBE fumes. United States production of TBA in 1991 was estimated at 2,990 billion pounds.

KEY TOXICOLOGIC EFFECTS

Acute Toxicity

The acute toxicity of TBA is low. The oral LD_{50} in the rat is 3500 mg/kg (Schaffarzick and Brown, 1952) and in the rabbit is 3,600 mg/kg (Munch, 1972). In the mouse the LD_{50} by intraperitoneal administration (i.p.) is 441 mg/kg (Maickel and McFadden, 1979). TBA vapors may be irritating to skin, eyes, nose and throat. Inhalation of vapors may cause dizziness, nausea, headache, fatigue, and weakness in the arms and legs. Inhalation of TBA vapors may also cause severe irritation of the respiratory system and narcosis.

Chronic Toxicity

An NTP two-year bioassay was conducted in Fischer 344 rats and $B6C3F_1$ mice exposed to TBA in drinking water (NTP, 1994; Cirvello et al., 1995). Groups of 60 F-344 rats were administered daily doses via drinking water of approximately 0, 85, 195, and 420 mg/kg-d in males and 0, 175, 330, and 650 mg/kg-d in females. Ten animals in each group were sacrificed at 15 months for evaluation; the remainder was exposed until the study was terminated at 103 weeks. The high dose groups of both sexes experienced decreased survival. Dose related decrease in body weight gain was also observed. All treated groups of females showed a dose-related increase in kidney weight at the 15-month evaluation. Males exhibited increased kidney weight at the mid and high doses. Nephropathy was seen in all groups of treated females and caused early mortality in high exposure groups. The study did not identify a NOAEL for chronic TBA toxicity in the rat. Groups of 60 B6C3F1 mice of each sex were administered TBA in drinking water at doses of approximately 0, 535, 1035, and 2065 mg/kg-d in males and 0, 510, 1015, and 2105 mg/kg-d in females. Reduced survival was observed in the high dose groups. Thyroid follicular cell hyperplasia was significantly increased in all exposed males and in females at the two higher doses. No NOAEL was identified for chronic TBA toxicity in the mouse.

Carcinogenicity

At the 24 month termination of the NTP rat bioassay, combined adenoma and carcinoma of the renal tubules was found in 8/50, 13/50, 19/50, and 13/50 of the control, low, mid and high dose males, respectively. The two-year survivals were 10/50, 6/50, 4/50, and 1/50, respectively. The increased incidence in the mid dose group was statistically significant ($p = 0.01$) by Fisher's exact test. The increased mortality in the high dose group may have reduced the observed incidence of renal tumors. Renal tubule hyperplasia was elevated in all treatment groups. Although no renal (or other) tumors were observed in female rats, the incidence of renal hyperplasia was significantly elevated in the high dose group. No renal tubule adenoma or carcinoma was observed in 227 control male rats in the four studies comprising the recent NTP historical control database for drinking water studies indicating the rarity of these neoplasms in male rats. The pathogenesis of proliferative lesions of renal tubule epithelium is thought to proceed from hyperplasia to adenoma to carcinoma (Cirvello et al., 1995). The incidence of renal tubule hyperplasia, adenoma and carcinoma were increased in all treated male groups and in controls compared to historical controls.

In the mouse NTP bioassay incidence of thyroid follicular cell hyperplasia was significantly elevated in all treatment groups of males (5/60, 18/59, 15/59, 18/57) and in the mid and high dose groups of females (19/58, 28/60, 33/59, 47/59). Follicular cell adenomas were significantly higher in high dose females (9/59). Chronic urinary bladder inflammation was seen in both sexes at the high dose, but no urinary bladder neoplasias were observed.

In conclusion, the increased incidence of renal tubule adenoma or carcinoma, combined, in male rats and of thyroid gland follicular cell adenoma in female mice is evidence of a carcinogenic response to TBA.

TBA has been reported as negative in the *Salmonella typhimurium* mutagenicity test, in a chromosome aberrations test in cultured Chinese hamster ovary (CHO) cells, in a sister chromatid exchange test in CHO cells, and in a mutation test in cultured mouse lymphoma cells (Gold et al., 1997).

Reproductive and Developmental Toxicity

No animal studies designed to specifically evaluate reproductive effects of TBA were found. NTP (1994) noted no ovarian histopathology at 20 mg TBA/L in a two year study, however, degeneration of the germinal epithelium of the testes was observed. Anderson et al. (1982) observed that 87 mM TBA did not affect the ability of mouse sperm to fertilize in vitro. No human data were located on the reproductive effects of TBA.

Faulkner et al.(1989) evaluated the developmental toxicity of TBA in two strains of mice exposed orally to 10.5 mmol/kg every 12 hr for days 6-18 of gestation. An increase in resorptions was observed but no malformations, variations, fetal weight effects, or strain differences were seen. In a rat study (Abel and Belitzke, 1992), oral TBA from gestation day eight to parturition at 0, 0.65, 1.3, and 10.9% in diet produced reductions in maternal weight gain, birth weights, and litter sizes (from 11 to 3 pups per litter) as well as reduced weight at

weaning and increased perinatal mortality (from 2% to 14%) and postnatal mortality (from 6% to 100%). Malformations were not described and the study was only reported in an abstract. Nelson et al. (1989) exposed rats to TBA by inhalation at 0, 2000, 3500, or 5000 ppm seven hours per day on gestation days 1-19. Decreases in maternal weight gain and fetal weight and increases in narcosis and ataxia were observed, but no effects were seen on resorptions, live litter size, or malformations. An increase in delayed ossification was seen and categorized as a variation.

Daniel and Evans (1982) administered TBA to Swiss Webster mice at up to 1% in the diet and observed decreases in maternal weight gain, fertility, live litter size, and pup weight on postnatal day two, and an increase in stillbirths. At the two highest doses there were significant behavioral effects including cliff avoidance, righting reflex, and open field activity. In an inhalation study where Sprague-Dawley rats were exposed to 6000 or 12,000 mg/m^3 TBA for seven hr per day on gestation days 1-19, no effects were noted on neuromotor coordination, activity, and learning as well as lack of change in neurochemical parameters (Nelson et al., 1991).

DOSE-RESPONSE ASSESSMENT

The following table contains available health assessment values used by California regulatory programs for TBA.

Table 7. Health assessment values for tertiary butyl alcohol

	Health Assessment Value	**Reference**
Acute reference exposure level	NA	---
Proposed chronic reference exposure level	NA	---
Cancer potency factor	3.0×10^{-3} (mg/kg-d) $^{-1}$	OEHHA (1999d)
Unit risk factor	NA	---
No significant risk level (NSRL)	NA	---
U.S. EPA reference dose (RfD)	NA	---
U.S. EPA reference concentration (RfC)	NA	---
Permissible Exposure Limit 8 hr (PEL)	100 ppm, 300 mg/m^3	OSHA (1998)
Short Term Exposure Limit (STEL)	150 ppm, 450 mg/m^3	OSHA (1998)
Threshold Limit Value (TLV/TWA)	100 ppm, 300 mg/m^3	ACGIH (1991)
Action Level for California drinking water (Health & Safety Code Sec. 116445)	0.012 mg/L	OEHHA (1999d);

NA = not available

TOLUENE
(CAS No. 108-88-3)

INTRODUCTION

Toluene is an aromatic solvent widely used in paint thinners, as a component of gasoline, and as an intermediate in the synthesis of other chemicals. About 6 billion pounds are produced each year (HSDB, 1998). The high volatility of toluene results in rapid evaporation from the liquid phase. Its low water solubility and low soil binding means that it also evaporates relatively rapidly from surface water or soils. Because it is relatively transparent to UV radiation, it is not photodegraded in air; however, it reacts with hydroxyl radicals to yield a half-life of a few hours to a day. It is microbially degraded in soils and groundwater with a half-life of a few days, but can persist much longer under anaerobic conditions and at high concentrations when microbial degradation is inhibited (particularly when liquid phase is present). Toluene is relatively mobile in soil. It does not bioconcentrate in sediment, plants, or animals (HSDB, 1998).

Toluene reaches the environment by vapor emission from chemical manufacturing, including fuel production, by evaporation from motor vehicles and tail-pipe emissions, from leaking fuel storage tanks, and from drying of oil-based paints and solvents. It is commonly detected in both rural and urban ambient air. Median concentrations in air of about 1 ppb in rural or remote areas, and 5 to 10 ppb in urban areas are common. Maximum urban air concentrations can reach more than 1,000 ppb (Singh et al., 1981). The time course of the toluene variations and the toluene/benzene ratios indicate that automobiles are the most common source of atmospheric toluene (HSDB, 1998; citing Termonia, 1982; Sexton and Westberg, 1980; Tsani-Bazaca, 1982). Toluene is also detected in drinking water supplies, usually at concentrations below 1 ppb. In a survey of finished drinking water from groundwater sources, toluene was detected in <5% of the samples, while it was detected in 19% of the samples of drinking water derived from surface water (Dyksen and Hess, 1982; Coniglio, 1980).

KEY TOXICOLOGIC EFFECTS

Acute Toxicity

Inhalation exposure to high levels of toluene causes headaches and eye and respiratory irritation. Excitability followed by sedation is observed in animal exposure studies. With prolonged high exposures (>10,000 mg/m^3, or 2500 ppm), narcosis, then death can occur. Drinking pure toluene can cause the same systemic toxic effects. Toluene also has been purposely inhaled as an intoxicant, which has resulted in neurotoxicity and kidney damage. Severe acute toxicity from exposure to toluene in drinking water is unlikely because of the solubility limit mentioned above (0.067%).

Chronic Toxicity

Prolonged exposures to toluene result in decreased body weight and increased liver weight (NTP, 1990), the parameters used by U.S. EPA for risk assessment (U.S. EPA, 1999b). Decreased

thymus weight in a subchronic study (Hsieh et al., 1989) represents a more sensitive index of toxicity than observed in chronic studies. Alterations of immune parameters were also observed. Therefore the latest OEHHA assessment of chronic hazard (OEHHA, 1999g) is based on the Hsieh subchronic study in mice, with a lowest observed adverse effect level of 105 mg/kg-day, and a no observed adverse effect level of 22 mg/kg-day for toluene supplied in drinking water.

Carcinogenicity

In several animal studies, no evidence of carcinogenicity of toluene has been observed in either mice or rats. Most genotoxicity analyses are negative. There is also no evidence in humans to suggest carcinogenicity. Toluene is not considered to be a carcinogen.

Reproductive and Developmental Toxicity

Animal studies provide clear evidence of developmental toxicity of toluene (Donald et al., 1991), including fetal growth inhibition and retardation of skeletal development. Deleterious effects occur with higher doses than the effects above, so health-protective levels are not based on these effects (OEHHA, 1999g). There is some evidence of possible adverse reproductive effects of toluene in humans (Arnold et al., 1994; Taskinen et al., 1994), but the data are not suitable for deriving safe exposure levels for risk assessment. Toluene is listed as a developmental toxicant by the State of California under Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986.

DOSE-RESPONSE ASSESSMENT

Toxicity of toluene is lower than that of many other organic solvents. The rapid metabolism to hippuric acid and excretion avoids the pathways for formation of reactive metabolites that occur with benzene, its close structural relative. The following table contains available health assessment values used by California regulatory programs for toluene.

Table 8. Health assessment values for toluene.

	Health Assessment Value	Reference
Acute reference exposure level (REL)	37 mg/m^3	OEHHA (1999a)
Proposed chronic reference exposure level	0.4 mg/m^3	OEHHA (1997a)
Cancer potency factor	NA	---
Unit risk factor	NA	---
Acceptable intake level (Prop. 65)	7 mg/day oral 13 mg/day inhalation	OEHHA (1994b)
No significant risk level (NSRL; Prop. 65)	NA	---
U.S. EPA reference dose (RfD)	0.2 mg/kg-day	U.S. EPA (1999b)
U.S. EPA reference concentration (RfC)	0.4 mg/m^3	U.S. EPA (1999b)
Public health goal (PHG)	150 ppb	OEHHA (1999g)

NA = not available

XYLENES

CAS No.: 1330-20-7 *(technical grade; a mixture of o-, m-, and p-xylene)*
95-47-6 *(ortho-xylene, o-xylene)*
106-42-3 *(para-xylene, p-xylene)*
108-38-3 *(meta-xylene, m-xylene)*

INTRODUCTION

Mixtures of o-, p- and m-xylenes are extensively used in both the chemical and petroleum industries. In the chemical industry, xylenes are used as solvents for products including paints, inks, dyes, adhesives, pharmaceuticals, and detergents. In the petroleum industry, xylenes are used as antiknock agents in gasoline and as intermediates in synthetic reactions. Exposures to xylenes from use in gasoline come from tailpipe emissions (i.e., emissions of unburned fuel), as well as from fugitive emissions.

Xylenes (isomers and mixtures) are regulated as toxic air contaminants in California under AB 1807 and are monitored by the statewide CARB toxics monitoring network.

KEY TOXICOLOGIC EFFECTS

Acute Toxicity

Despite its structural similarity to benzene, xylene does not influence hematopoiesis. In humans, the principal systemic effects of acute xylene exposure are on the central nervous system, but it is also a respiratory and eye irritant. A no-observed-adverse-effect level (NOAEL) for humans based on eye irritation has been estimated to be approximately 100 ppm for at least a 30-minute exposure (OEHHA, 1999a; based on data from the following sources: Nelson et al., 1943; Carpenter et al., 1975; Hastings et al., 1984).

From studies of experimental animals, LC_{50} values (i.e., the air concentrations lethal to 50% of a test population) have been reported for rats and mice. Six-hour LC_{50} values in mice for each xylene isomer are: 4,595 ppm (19,942 mg/m^3), 5,267 ppm (22,859 mg/m^3) and 3,907 ppm (16,956 mg/m^3) for o-, m-, and p-xylene, respectively (Bonnet et al., 1979). A four-hour LC_{50} for mixed xylenes was estimated as 6,700 ppm (29,078 mg/m^3) in rats (Carpenter et al., 1975). In rats, acute xylene exposure has been noted to cause changes in liver (i.e., increased liver weight, changes in cytochrome P450 content and activity, decreased liver glutathione concentrations), as well as changes in lung (i.e., microsomal membrane damage, decreased P450 content, inhibition of aryl hydrocarbon hydroxylase and CYP2B1 activities) (OEHHA, 1999a).

Chronic Toxicity

Information on the chronic toxicity of xylenes to humans is almost exclusively limited to studies of occupational exposures in which persons usually inhaled a mixture of hydrocarbon solvents. However, chronic xylene exposure has been associated with effects in a number of organs and organ systems, including: lungs (e.g., labored breathing, impaired pulmonary function), skin and

eyes (irritation), neurological system (headache, dizziness, irritability, weakness, slowed reaction time, decreased muscle coordination, confusion, impaired short-term memory, anxiety); heart (abnormal electrocardiogram, palpitations), gastrointestinal system (nausea, vomiting, gastric discomfort), and possibly the reproductive system (discussed below). Of the few available chronic studies in animals, none comprehensively examined systemic effects (OEHHA, 1999c). An inhalation study by Tatrai et al. (1981) provides a lowest-observed-adverse-effect level (LOAEL) for body weight gain in male rats of 1096 ppm o-xylene.

Carcinogenicity

No exposure studies were located that specifically examined the carcinogenic effects of xylene in humans. No inhalation exposure studies were located that examined the carcinogenic effects of xylene in experimental animals. In an oral carcinogenicity study, rats and mice were administered mixed xylenes by gavage in corn oil 5 days/week for 103 weeks (NTP, 1986). Mice received daily doses of 500 or 1000 mg/kg, and rats received daily doses of 250 or 500 mg/kg. There was no evidence for treatment-related carcinogenicity.

Reproductive and Developmental Toxicity

Reproductive effects were documented by Taskinen et al. (1994) who found increased incidence of spontaneous abortions in 37 pathology and histology workers exposed to both xylene and formaldehyde in the work place. The multiple chemical exposures and the small number of subjects in this study limit the conclusions that can be drawn as to reproductive effects of xylene in humans (OEHHA, 1999c).

Developmental effects, including reduced fetal weights and ossification defects in bones of the skull, have been documented in offspring of animals exposed to xylenes while pregnant. It appears that all three isomers of xylene are fetotoxic and that many of the fetotoxic responses are secondary to maternal toxicity. However, there is inconsistency among the various studies as to the concentrations of xylene producing developmental effects and of those producing no developmental effects (OEHHA, 1999a and 1999c; ATSDR, 1995).

Xylenes are not listed as reproductive or developmental toxicants by the State of California under Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986.

DOSE-RESPONSE ASSESSMENT

The following table contains available health assessment values used by California regulatory programs for xylenes.

Table 9. Health assessment values for xylenes

	Health Assessment Value	Reference
Acute reference exposure level (REL)	22000 μ/m^3	OEHHA (1999a)
Proposed chronic reference exposure level	700 μ/m^3	OEHHA (1999c)
Cancer potency factor	NA	---
Unit risk factor	NA	---
No significant risk level (NSRL)	NA	---
U.S. EPA reference dose (RfD)	2E+0 mg/kg-day	U.S. EPA (1987)
U.S. EPA reference concentration (RfC)	NA	---
Public health goal	1.8 mg/L	OEHHA (1997c)

NA = not available

Since adopted health assessment values suitable for assessing chronic environmental exposures to xylenes are not available, OEHHA used the proposed chronic reference exposure level (REL) for the purpose of this report. The proposed chronic REL is currently being developed under the Air Toxics Hot Spots Program risk assessment guidelines process (Senate Bill 1731, Statutes of 1992, Ch. 1162 of the California Health and Safety Code). The methodology used to derived the proposed chronic REL for xylenes, as well as the number itself, have undergone an initial round of public and scientific peer review, and are currently being considered by the State's Scientific Review Panel. The derivation of the chronic REL is summarized below, and detailed in OEHHA (1999c).

Derivation of the Proposed Chronic Reference Exposure Level

The proposed chronic REL is based on an epidemiologic investigation of workers exposed to xylene solvents (Uchida et al., 1993). The study population consisted of 175 men and women exposed to 14.2 ± 2.6 ppm mixed xylenes (geometric mean) for an average 7 years. The control population consisted of 241 men and women. A dose-related increase in the prevalence of eye irritation, sore throat, floating sensation, and poor appetite was reported. A lowest-observed-adverse-effect level (LOAEL) of 14.2 ppm was identified. A no-observed-adverse-effect level (NOAEL) was not obtained from this study.

While the Uchida et al. (1993) study was based on occupational exposures, the chronic REL is intended to protect the general public who could be exposed continuously. Therefore, an equivalent time-weighted average concentration (C_{AVE}) was estimated from the observed concentration (C_{OBS}) as follows:

$C_{AVE} = C_{OBS} \times (10\ m^3/day\ occupational\ exposure\ /\ 20\ m^3/day\ total\ exposure) \times (5\ days\ /\ 7\ days)$

In addition, a cumulative uncertainty factor of 30 was applied, 3 for LOAEL to NOAEL extrapolation and 10 for sensitive persons within the population. Therefore:

Proposed chronic REL = C_{AVE} / UF = 0.17 ppm (170 ppb; 0.7 mg/m^3; 700 μg/m^3)

The same study (Uchida et al., 1993) was used to derive the public health goal (PHG) of 1.75 mg/L for xylenes in drinking water (OEHHA, 1997c).

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